REMARKS

Claims 16-22 and 25-28 are pending in this application. By this amendment, applicants have amended claim 16 to better recite applicant's invention. Support for the amendment to claim 16 may be found in the specification *inter alia* at paragraphs 0001, 0040, 0049, and 0050. Accordingly, applicants respectfully request that the Examiner enter and consider this amendment.

Rejection Under 35 USC § 102

The Examiner rejected claims 16-22 and 25-28 under 35 U.S.C. 102(e) as anticipated by Pacioretty and Babish, U.S. Application Publication No. 2004/0106591.

In response, applicants have amended claim 16 to recite that DHA is present in the administered composition "as the only active substance". This clearly indicates that the composition used in the method of applicant's invention contains only one active ingredient, i.e. docosahexaenoic acid (DHA). Examples 1 and 2 at paragraphs 0040, 0049 and 0050 disclose the "administration of DHA" alone so that the purpose of the present invention is to administer DHA and not a mixture of different active ingredients as disclosed in Pacioretty and Babish.

Pacioretty and Babish does not teach each and every element of amended claim 16 and clearly teaches away from the present purpose by disclosing the use of a combination of active ingredients understanding then that the effect of said combination is not the addition of each component effect, and therefore not the same effect provided in the present invention. Although, at paragraph 0059 of Pacioretty and Babish, DHA is mentioned as one of the possible conjugated fatty acids, this conjugated acid is **always** combined with other active ingredients. In all the examples and in the last paragraph by way of conclusion, Pacioretti and Babish state that "there has been disclosed a formulation containing, as a first active component, a conjugated fatty acid or conjugated alcohol and, as a second component at least one member selected from the group of thiol-containing compounds and bioavailable trivalent chromium compounds." In addition, Pacioretty and Babish do not use DHA alone or in combination in any of the examples shown. This fatty acid is only contemplated as a possibility in the long list of 20 acids provided in paragraph 0059 and not even considered as a preferred option.

Accordingly, it is clear that Pacioretti and Babish does not disclose or suggest the administration of DHA alone but rather teaches the administration of DHA with a thiol-containing compound or a trivalent chromium. Applicant's invention as now recited in amended claim 16 clearly is a method wherein DHA is administered as the only active ingredient. Accordingly, Paccioretti and Babish does not teach each and every element of amended claim 16 and therefore does not anticipate amended claim 16 or any claims dependent therefrom.

In addition, applicant notes that the term "active ingredient" or "active substance as used in the present invention is defined according to the Food and Drug Administration as follows:

"According to 21 CFR 210.3(b)(7), an active ingredient is any component of a drug product intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of humans or other animals. Active ingredients include those components of the product that may undergo chemical change during the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." (Emphasis added)

The fact that combined active ingredients provide a different effect from that corresponding to the addition of effects due to each of the active ingredients is also supported by the attached document from the European Commission.

In particular, it states:

> If a simultaneous administration of more than one pharmacologically active substance is justified, an administration in the form of a fixed combination product generally simplifies therapy; however, a fixed combination product cannot be justified by the simplification of treatment alone. Therefore a fixed combination must provide an advantage over and above that which can be obtained by the use of monosubstance preparations.
>
> Only in exceptional cases should fixed combination products be used in the treatment of diseases in which a careful individual titration is required.
>
> For any individual fixed combination product it will be necessary to assess the potential advantages in the clinical situation against possible disadvantages in order to determine whether the particular combination of active ingredients is justified and whether the product meets the requirements of the state of the art with respect to efficacy and safety. For antimicrobials and anthelmintics, a fixed combination of more than two active ingredients is unlikely to be justifiable.

Rejection Under 35 USC § 103

The Examiner rejected claims 16-22 and 25-28 under 35 U.S.C. 103(a) as unpatentable over Holstein et al. in view of Connor et al. In making this rejection, the Examiner indicates that hyperlipidemia can be considered as a form of lipodystrophy. Applicant respectfully traverses this ground of rejection and insists on the difference between hyperlipidemia and lipodystrophia.

Lipodystrophy disease is defined in the present application at paragraphs 0007 and 0008 which state that "the patients show loss of fat in the face, buttocks, extremities and thorax, accompanied by accumulation of fat inside the abdomen, the back of the neck and in the breast area in women, together with increase plasmatic levels of cholesterol, triglycerides, lowering of HDL cholesterol (protective cholesterol) and increase of LDL cholesterol (harmful cholesterol), insulin resistance (occasionally diabetes) and occasionally arterial hypertension. This entire set of situations is known as lipodystrophy syndrome." (Emphasis added)

Lipodistrophy in patients who are receiving a HAART treatment is not merely an alteration in the body-fat distribution but a multifactorial illness wherein not only the metabolism of fatty acids is involved but also the metabolism of glucids. Applicant submits as evidence a Drug Watch article highlighted to point the Examiner's attention to the definition of lipodystrophy. Specifically, applicant notes the passage stating that "[m]etabolic abnormalities include increased blood lipid (fat) levels and insulin resistance (inability of cells to properly use insuline, leading to blood sugar imbalances). (Emphasis added)

Accordingly, hyperlipidemia cannot be regarded as a form of lipodistrophy since the effects are not the same. Hyperlipidemia consists of the presence of raised or abnormal levels of lipids and/or lipoproteins in the blood. Hyperlipidemia usually has no noticeable symptoms and tends to be discovered during routine examination or evaluation for atherosclerotic cardiovascular disease. The Examiner even admits that hyperlipidemia is almost always associated with lipodystrophy which means that there are even few cases where they are not related. See the enclosed NCBI database document showing the classification of lipid metabolism disorder

wherein hyperlipidemia is not under the heading of lipodystrophy, thereby being considered as different conditions.

Neither Holstein et al nor Connor et al. teach applicant's invention alone or in combination. Connor et al. teach the effect of dietary n-3 fatty acids from fish and fish oil in hypertriglyceridemic patients with combined hyperlipidemia (abstract). Being hyperlipidemia alone, or hypertriglyceridemia combined with hyperlipidemia, two clinical conditions different from lipodystrophy, there is no suggestion in Connor et al. that dietary n-3 fatty acids could be as well effective in lipodystrophy. It was certainly not obvious for the skilled in the art from the teachings of either Holstein et al. or Connor et al, that the administration of DHA as the only active substance would be effective for example in increasing facial fat loss. As a matter of fact, there are yet no drugs currently approved for the treatment of lipodystrophy. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Reconsideration and allowance of all the claims herein are respectfully requested.

Respectfully submitted,

June 25, 2010

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FIXED COMBINATION PRODUCTS

Guideline Title	Fixed Combination Products
Legislative Basis	Directive 81/852/EEC as amended
Date of First Adoption	May 1991
Date of Entry into Force	November 1991
Status	Last revised May 1991
Previous Titles	None
Other References	III/3730/90
Additional Notes	This note for guidance concerns the application of Part 4, Chapter III of the annex to Directive 81/852/EEC as amended with a view to the granting of a marketing authorisation for a medicinal product.

CONTENTS

FIXED COMBINATION PRODUCTS

1. JUSTIFICATION

If a simultaneous administration of more than one pharmacologically active substance is justified, an administration in the form of a fixed combination product generally simplifies therapy; however, a fixed combination product cannot be justified by the simplification of treatment alone. Therefore a fixed combination must provide an advantage over and above that which can be obtained by the use of monosubstance preparations.

Only in exceptional cases should fixed combination products be used in the treatment of diseases in which a careful individual titration is required.

For any individual fixed combination product it will be necessary to assess the potential advantages in the clinical situation against possible disadvantages in order to determine whether the particular combination of active ingredients is justified and whether the product meets the requirements of the state of the art with respect to efficacy and safety. For antimicrobials and anthelmintics, a fixed combination of more than two active ingredients is unlikely to be justifiable.

Potential advantages of fixed combination products include:

1.1 Improvement of activity

At the same dose the therapeutic effect can be improved by synergistic or additive actions by various mechanisms, or tolerance can be improved by reducing the dose of the individual ingredients.

1.2 Broadening of the activity spectrum

Broadening the activity spectrum often relies on:

a) the simultaneous control of several aetiological factors which have been confirmed to occur simultaneously and therefore are to be controlled simultaneously (e.g. mastitis-metritis-agalactic complex in sows, etc.), or

b) the addition of a symptomatically active substance, which has been confirmed to improve the clinical result and which does not result in adverse interactions.

Fixed combinations may be regarded as rational if the half life or duration of action of the active ingredients do not differ significantly; this may not necessarily apply where it can be shown that the fixed combination is clinically valid despite differences in this respect.

1.3 Improvement of pharmacokinetic properties

The intensity and duration of the action of a substance can be improved if bioavailability is increased or metabolic inactivation or elimination is reduced by another substance. Combination with a substance which speeds up the action of another ingredient of the combination or delays its absorption may also be rational.

2. INDICATIONS

The indication(s) claimed for a fixed combination product should be such that each active ingredient contributes to the overall therapeutic effect of the product. The fixed combination product should be formulated so that the dose and proportion of each active ingredient present are appropriate to all the recommended uses.

3. EFFICACY AND SAFETY

Both the efficacy and safety of a fixed combination product and its active ingredients should have been investigated in the animal species for which it is intended.

If one active ingredient has no inherent therapeutic effect but just enhances or complements the activity of the other one (e.g. beta-lactams + beta-lactamase inhibitors) or if one active ingredient is active for aetiologic and the other one for symptomatic reasons (e.g. antibiotic + mucolytic), it should be demonstrated that the active ingredient without direct therapeutic efficacy produces the expected effect (e.g. enhances the activity, etc.). For example, it is considered sufficient to demonstrate that:

a) The fixed combination shows a superiority over the main component if given alone, whatever the nature of this superiority be (pharmacodynamic, pharmacokinetic, safety or clinical).

b) The active ingredients of a fixed combination product do not reduce effects of each other, unless this is precisely the objective of the fixed combination, e.g. to minimise an undesirable effect. Evidence of this should be provided as far as possible by *in vitro* or *in vivo* pharmacodynamic or pharmacokinetic tests.

c) The active ingredients of a fixed combination do not interfere with their respective intrinsic safety, except where the benefit/risk ratio assessment is still positive.

For fixed combinations of antimicrobials and antiparasiticides an assessment of the potential for the development of resistance will be necessary.

For fixed combination products of vitamins, oligoelements and minerals, it may be difficult to establish the interest of each active ingredient. Therefore, such combinations are accepted as being effective and safe if the indications claimed are restricted to deficiency diseases where treatment by a fixed combination is justified and the maximum doses do not exceed internationally and scientifically accepted limits. This exemption is possible for fixed combination products containing solely vitamins, oligoelements and/or minerals (e.g. combinations of vitamins and antibiotics are not covered by the exemption).

A fixed combination of electrolytes and nutrients may also be exempted from the requirements of this guideline. In fact, any experimental evidence comparing the separate activities of each of these ingredients is irrelevant as the combination of different components in a solution for fluid therapy is justified by the parallel losses and imbalances quantified in the animal suffering from dehydration (see also the note for guidance *Veterinary Medicinal Products for Fluid Therapy in Case of Diarrhoea*).

4. INTERACTIONS

The possibility of interactions between the active ingredients should always be considered and if necessary be investigated and documented, taking into account the formulation of the product.

There should not be any adverse interaction between the active ingredients or the other components of the fixed combination product (e.g. in the case of pharmaceutical incompatibilities or in case an active ingredient masks toxic effects of other ingredients).

5. WITHDRAWAL PERIODS

The period for which the pharmacologically active substances concerned remain in the animal's body must be demonstrated by appropriate investigations. For food producing animals, the withdrawal period should be determined on the basis of the active ingredient giving the longest period, after administration of the fixed combination product, within which residues of a type and quantity constituting a potential health hazard are likely to be found in foodstuffs produced from the treated animals.

6. COMBINATION PACKS

The principles applicable to fixed combination products will also be applied in the assessment of preparations consisting of different medicinal products in combination packs. Combination packs contain a combination of several active ingredients made of distinct and/or different galenic formulations wholly included in a unique packaging. This kind of combination includes:

a) extemporaneous combinations to be used in a unique dosage after mixture;

b) Monosubstances to be used simultaneously but without previous mixture (e.g. hormonal treatments).

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1: Lipid Metabolism Disorders Links

Pathological conditions resulting from abnormal anabolism or catabolism of lipids in the body.
Year introduced: 2007

Subheadings: This list includes those paired at least once with this heading in MEDLINE and may not reflect current rules for allowable combinations.

blood chemically induced classification complications diagnosis diet therapy drug therapy enzymology epidemiology etiology genetics history immunology metabolism pathology physiopathology prevention and control surgery therapy ultrasonography urine virology

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Entry Terms:

- Lipid Metabolism Disorder
- Metabolism Disorder, Lipid
- Metabolism Disorders, Lipid

All MeSH Categories
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Nutritional and Metabolic Diseases
Metabolic Diseases
Lipid Metabolism Disorders
Dyslipidemias
Hyperlipidemias +
Hypolipoproteinemias +
Smith-Lemli-Opitz Syndrome
Lipid Metabolism, Inborn Errors
Lipidoses
Cholesterol Ester Storage Disease +
Neuronal Ceroid-Lipofuscinoses
Sjogren-Larsson Syndrome
Sphingolipidoses +
Lipodystrophy
HIV-Associated Lipodystrophy Syndrome
Lipodystrophy, Congenital Generalized
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Lipomatosis
Adiposis Dolorosa
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genes into cells is known as recombinant gene technology. The first version of recombinant human growth hormone (sometimes called rhGH) was made by Genentech of South San Francisco, California, and approved for sale by the U.S. Food and Drug Administration (FDA) in October 1985. Today several companies produce and market recombinant hGH under different brand names (see sidebar on this page).

Recombinant technology solved the problems of disease transmission and availability, but not of cost. HGH is extremely expensive—from several thousand dollars per year for limited supplemental use, to about $35,000 per year for a child who completely lacks the protein. The huge cost (and profit) of making the complex molecule has encouraged manufacturers to find other uses for hGH beyond the initial indication for children with stunted growth.

Pituitary tumors, chronic illness, side effects of therapy for other medical conditions, and processes associated with aging all can contribute to reduced pituitary function and decreased production of growth hormone. Expansion of the hGH market to treat such conditions was a natural outcome, and the FDA has approved label indications for new uses as manufacturers have submitted evidence of success from clinical trials.

At the same time, some proponents of hGH paint a dazzling but false portrait of the substance. Many sites on the Internet tout hGH as a panacea for everything from losing weight to halting the aging process. Some bodybuilders use growth hormone, often illegally, to rapidly increase muscle mass. Claims have proliferated though evidence to support them is scant. Growth hormone can be very beneficial for correcting a deficiency, but having too much of it does not necessarily bring added benefit—though it does increase the risk of side effects. Nevertheless, illicit use of hGH appears to be widespread.

HGH by Other Names

HGH (somatropin) is produced by several companies and sold under a number of brand names. The main distinction between them is that they are produced in different types of cell lines and have been evaluated in clinical trials for different indications. The FDA allows a company to claim a label indication only if it has conducted trials for a specific condition with that version of hGH. Most physicians, however, believe that the different versions of hGH have the same biological effects. The most common brands of hGH sold in the U.S. are:

Genotropin and Genotropin MiniQuick
manufactured by Pharmacia (Pfizer)

Humatrope
manufactured by Eli Lilly and Company

Norditropin
manufactured by NovoNordisk

Nutropin and Nutropin AQ
manufactured by Genentech

Protropin
manufactured by Genentech

Saizen
manufactured by Serono

Serostim
manufactured by Serono

AIDS Wasting

AIDS wasting syndrome (cachexia) is a condition associated with advanced HIV disease. It involves overall weight loss, but more importantly, the loss of lean body mass, or muscle, which sometimes may be replaced by fat. Weight loss results from a number of factors, alone or in combination, including lack of appetite, nausea, diarrhea, oral problems that make eating difficult, and problems related to intestinal absorption and use of nutrients. The condition was much more prevalent in the developed world before combination antiretroviral therapy became available.

A correct diagnosis and the proper intervention for each individual are as important in treating AIDS wasting as they are for any other medical problem. Early intervention is often most successful, and a variety of effective and relatively inexpensive tools (such as nutritional supplements, appetite stimulants, and exercise) can be used. HGH is not a universal remedy for treating AIDS wasting. While it can have a dramatically beneficial effect in some individuals (presumably those with a deficiency of natural hGH), the majority may see no benefit.

The current hGH regimen for AIDS wasting consists of a daily injection administered at bedtime to mimic the natural cycle of growth hormone release into the bloodstream. The dose is 4–6 mg, based upon body weight. HGH alone is likely to result in weight gain that is primarily fat, while adding a regimen of resistance exercise, such as weight training, can help build lean body mass. The average cost of hGH therapy for AIDS wasting is approximately $250 per day. Due to pressure from AIDS activists, Serono Laboratories, which produces a version of hGH known as Serostim, capped the cost of their hGH at $36,000 per calendar year for qualified individuals. The company provides the drug free of charge beyond this point.

Lipodystrophy

The term "lipodystrophy" is broadly applied to issues of body fat irregularities and metabolic abnormalities associated with HIV disease. It can include the wasting of fat from the face, arms, legs, and buttocks, as well as an increase in fat around the abdomen and on the upper back. Metabolic

"In broad terms, management approaches to lipodystrophy tend to be dictated by 'fashion' and perhaps 'marketing' rather than fact or science."

Graeme Moyle, MD

abnormalities include increased blood lipid (fat) levels and insulin resistance (inability of cells to properly use insulin, leading to blood sugar imbalances). There is little agreement on a measurable definition of lipodystrophy, which impedes research into the condition.

Consensus appears to have emerged, however, around the idea that there are likely several different biological mechanisms and various factors at play, either alone or in combination. Some of the manifestations of lipodystrophy may be associated with HIV infection itself, others with specific anti-HIV drugs, and still others with the natural processes of aging. The picture is further complicated by individual genetic factors, body chemistry, and lifestyle choices.

Successful strategies to treat the various manifestations of the syndrome have not been identified. "In broad terms, management approaches to lipodystrophy tend to be dictated by 'fashion' and perhaps 'marketing' rather than fact or science," writes Graeme Moyle, MD, of London's Chelsea and Westminster Hospital in the most recent *Medscape* treatise on the subject. Researchers are gathering scientific data to investigate the use of hGH for some symptoms of lipodystrophy—however curious it may seem to reverse increases in abdominal fat, for instance, with a drug that can promote fat gains in people with wasting.

Donald Kotler, MD, of St. Luke's-Roosevelt Hospital in New York City is the principal investigator of the most sophisticated study of hGH and lipodystrophy yet conducted. The trial is known as STARS—Serostim in the Treatment of Adipose Redistribution Syndrome (ARS is another proposed term for lipodystrophy). In late September Dr. Kotler presented the most recent results from the study at the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in San Diego.

The multicenter STARS trial randomized 239 HIV positive subjects (13% female, 20% non-Caucasian) with an abnormal waist circumference or waist-to-hip ratio (waist circumference divided by hip circumference) to take 4 mg hGH daily, 4 mg hGH every other day, or placebo for 12 weeks. Participants then entered a second 12-week phase during which those who had received daily hGH were randomized to receive placebo (27 subjects) or hGH on alternate days (23 subjects); those who began taking hGH on alternate days continued to do so (48 subjects); and the initial placebo group went on to take 4 mg hGH daily (53 subjects). Everyone received hGH at some point during the 24-week trial, but no one received it on a daily basis for more than half the trial.

Principal measurements for the trial were the reduction of visceral adipose tissue (VAT, which is firm, internal abdominal fat, not the soft fat that lies just beneath the skin); levels of non-HDL (non-high-density lipoprotein) cholesterol; insulin resistance; lean body mass; and self-assessed quality of life and body image. Increased VAT, elevated non-HDL cholesterol, and insulin resistance are risk factors for cardiovascular disease. DEXA scanning technology was used to measure internal VAT. Mean (average) age at baseline was 45; mean body mass index (calculated as weight divided by height squared) was 27 kg/m^2. Average baseline VAT was 331 cm^2 in men and 249 cm^2 in women, which was significantly greater than in healthy control subjects of similar sex and age.

Dr. Kotler's group found that daily use of hGH was necessary to achieve a statistically significant reduction of visceral fat (at least at the 4 mg dose) in the 151 subjects who completed 24 weeks. Switching to alternate-day use after initial daily use was sufficient to keep internal fat from returning, but if hGH was stopped completely, the fat came back. At 24 weeks, people who received daily hGH then placebo showed a mean reduction in VAT of 22.4 cm^2; those who stayed on alternate-day dosing for the full 24 weeks had a mean reduction of 19.7 cm^2; those taking placebo followed by daily hGH lost a mean of 30.5 cm^2; and subjects who began taking daily hGH and continued on an alternate-day regimen had a mean reduction of 30.9 cm^2 of VAT. DEXA scanning showed that these reductions were primarily in trunk fat, not in the limbs. For the four groups mentioned above, the VAT fat losses were 1.9, 3.0, 3.5, and 5.0 lbs, respectively. Loss of limb fat was 0.2, 0.4, 1.1, and 1.5 lbs, respectively, with an average loss of about 0.25 lbs per limb.

HGH reduced non-HDL cholesterol levels in all groups, with the decline ranging from 6.6% to 8.4%. The greatest benefit came with daily dosing followed by alternate-day maintenance dosing. Those who were later switched to placebo saw their non-HDL cholesterol levels start to climb again, though levels were still below baseline 12 weeks after stopping the hGH injections.

Serono Laboratories' patient assistance program, which provides hGH for AIDS wasting for compassionate use and support above the $36,000 annual cap, can be contacted at 888-628-6673.

With regard to insulin resistance, the three arms of the trial that started on hGH showed an identical pattern of an increase in mean area under the curve (AUC) serum insulin through week 12, then a significant decline toward baseline by week 24. (AUC here refers to total insulin concentration over a period of time.) The arm that started on placebo showed no increase until hGH was initiated; this group was not tracked long enough to note a decline. However, AUC insulin levels tend to correlate poorly with true measures of insulin sensitivity.

Dr. Kotler concluded that the reduction of VAT, the decrease in total and non-HDL cholesterol levels, and the return of insulin levels to baseline by the end of the study suggest that hGH therapy could lead to a reduction of cardiovascular disease risk in this population. Nevertheless, it is important to remember that these results are from limited clinical trials. No version of hGH is approved by the FDA for treatment of lipodystrophy. While physicians have the flexibility to prescribe off-label (unapproved) use of hGH, health insurance providers most often will pay for only label-indicated uses of a drug, and few people can afford to pay for hGH out of their own pockets.

Thymic Function

New evidence suggests that hGH also may enhance immune system restoration and HIV-specific T cell responses. At the XIV International AIDS Conference in Barcelona, Spain, this past summer, researchers from Chelsea and Westminster Hospital presented data showing a direct effect of hGH on thymic function in a very small group of people with chronic HIV infection taking antiretroviral therapy. The thymus, a lymphoid organ located behind the upper breastbone, is the site of T cell maturation and differentiation—that is, where these white blood cells learn to recognize antigens (substances that stimulate an immune system response).

After 12 weeks of hGH administration (4 mg per day), 11 of 12 subjects in this study showed significant increases in naive CD4 and CD8 cell counts, indicating boosted thymic activity. Naive T cells are necessary for immune reconstitution, as memory T cells are programmed to target previously encountered antigens and do not respond to new pathogens introduced into the body (for example, those causing certain opportunistic illnesses, or OIs). In addition, HIV-specific memory CD4 and CD8 responses were significantly improved in at least nine of the 12 subjects after 12 weeks of hGH therapy. The memory CD4 response, however, was sustained only in those who continued taking daily hGH (instead of alternate-day or twice-weekly dosing) through week 24.

While these recent data are intriguing, much more study is needed. Even if it proves viable, clinical use of this potential new indication for hGH is likely years away.

Risks and Side Effects

Because hGH is a protein that would be destroyed in the stomach and intestines by digestive enzymes, it cannot be taken as a pill and must be injected subcutaneously (under the skin).

Like sidewalk vendors selling $20 Rolex watches, Internet sites offer cut-rate growth hormone prices that often are too good to be believed—and should not be.

HGH should not be taken by people with acute critical illness due to complications of open heart or abdominal surgery, multiple accidental trauma, or acute respiratory failure. HGH may stimulate the growth of active tumors and should not be used by people who have cancers that are not under control. HGH also may affect blood triglyceride levels and may increase the risk of developing diabetes in those who are already at risk, particularly people who are obese. Individuals taking insulin may need to have their doses adjusted. In spite of Dr. Kotler's findings, there may be increased cardiovascular risk with long-term hGH use, perhaps related to insulin resistance. Studies of growth hormone have not been conducted in pregnant women.

Up to 50% of all people experience mild to moderate musculoskeletal discomfort when starting hGH, and about 25% experience some fluid retention and swelling of the hands and feet. While both generally decrease as the body becomes accustomed to the drug, a significant number of people must stop taking hGH due to these side effects. Some people develop carpal tunnel syndrome (CTS, a condition characterized by numbness, pain, or tingling in the wrists or hands) while taking hGH; CTS typically resolves when the drug is discontinued. Other possible side effects include nausea, diarrhea, flu-like symptoms, and chest pain; only rarely are these severe enough to require discontinuation of treatment.

Dollars and Fraud

The high price tag and potential off-label and illegal uses of hGH appear to be strong incentives for criminal activity by corporations and individuals alike. Genentech illegally promoted off-label use of hGH in the first decade after it was approved. The FDA sued, and in 1994 the company agreed to pay a $50 million fine for the violations.

In late 2001 Phoenix, Arizona, witnessed a complex web of false drug orders, a bungled hijacking, theft, arson, insurance fraud, and murder over a shipment of hGH. A wholesale value of about $1 million and a street value three times that amount set these events in motion.

Counterfeiting of hGH is a growing problem. Like sidewalk vendors selling $20 Rolex watches, Internet sites offer

cut-rate growth hormone prices that often are too good to be believed—and should not be. But counterfeit drugs can also enter the regular distribution chain, complete with knock-off packaging and bogus manufacturing lot numbers. In January and May 2001, and again in May 2002, Serono and the FDA warned about circulation of counterfeit Serostim distinguishable only by small variations in lot number and package design. Some of the counterfeits have little or none of the claimed active ingredient and they may contain dangerous impurities.

Serono—though apparently no other manufacturer of hGH—considers the problem so significant that it established the Serostim Secured Distribution Program. As of November 1, 2002, the distribution network has been restricted, and every single dose of Serostim has a number and is tracked directly to the patient. This helps to assure the quality of the drug. It also minimizes the likelihood of drugs being diverted and reduces the potential for reimbursement fraud.

Bob Roehr is a journalist and medical writer based in Washington, DC.

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